Docket No. 10914-11

PATENT

CERTIFICATE OF MAILING

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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Applicant:	Isa Odidi et al	:	Paper No.:
Serial No. :	09/403,437	:	Group Art Unit: 1615
Filed:	October 21, 1999	:	Examiner: A. Pulliam

For: **Controlled Release Formulations Using Intelligent Polymers**

DECLARATION UNDER 37 C.F.R. 1.132

Box Fee Amendment
Commissioner for Patents
Washington, DC 20231

Isa Odidi and Amina Odidi declare that:

1. They are coinventors of and are familiar with the present U.S. Patent Application Serial No. 09/403,437, and they are familiar with the Official Actions issued in the present application and the references cited by the Examiner, including U.S. Patent No. 3,870,790 to Lowey et al, U.S. Patent No. 5,162,117 to Stupak et al, and U.S. Patent No. 4,853,249 to Takashima et al.

2. In order to demonstrate significant and unexpected improvements exhibited by the controlled release pharmaceutical compositions defined by claims 1 and 30 in the present application, they conducted, or had conducted under their direction and control, certain experiments as described herein.

3. In one experiment, three compositions as described in Table 1 were prepared and studied for their model drug release properties. The three compositions respectively

contained hydroxypropylmethyl cellulose (HPMC), ethylcellulose (EC), and hydroxyethyl cellulose (HEC).

Table 1. Formulation of Model Drug Compositions Using Different Cellulose Derivatives

Formulation	HPMC 15%	HEC 15%	EC 15%
Model Drug	50%	50%	50%
Hydroxypropylmethyl cellulose	15%	0	0
Hydroxyethyl cellulose	0	15%	0
Ethylcellulose	0	0	15%
Lactose	44%	44%	44%
Magnesium stearate	1%	1%	1%

The purpose in this case was to optimally prepare a controlled release tablet using 15% weight/weight of a cellulose derivative capable of releasing not more than 18% of its drug content in 1 hour, not more that 50% of it drug content in 6 hours and not more that 70% of its content in less than 8 hours. As shown in Table 2 and the attached Figure 1, the compositions had significantly different controlled release properties.

Table 2. Results from Dissolution Studies of the Model Formulations

Time, hrs.	HPMC 15%	HEC 15%	EC 15%
0	0	0	0
1	16.9	60	88.1
2	25	68	88.2
4	43	75.6	88.3
5	50	78.4	88.4
6	53.4	80	88.5
7	63.3	83.5	88.6
8	66.5	83.2	88.6
10	78.4	88.8	90
11	80.4	87.5	90
12	81.2	84.7	90
13	89.7	90	90
14	92	90	90

For example, the amount of drug released in 1 hour is 17% for HPMC, 60% for HEC and 88% for EC. It was also observed that EC tablets broke up in about 30 minutes. The time taken for 70% of the drug to be released (i.e., $T_{70\%}$) was about 9 hours for HPMC, 4 hours for HEC and 30 minutes for EC. These results clearly indicate that HPMC, HEC and EC are not interchangeable, particularly in a controlled release pharmaceutical composition. These results are unexpected in view of the three patent references cited above.

4. In a further experiment, the effect of moisture content of compositions according to the invention in the form of granulations and tablets on (i) Geometric mean granule diameter, (ii) Hausner ratio, (iii) Compressibility index, (iv) Friability, (v) Tablet hardness, and (vi) Tap density, was studied. The results are set forth in the attached Figures 2-7, and overall, the results indicate that the higher the moisture content, the less desirable characteristics are provided for the compositions.

5. With respect to Figure 2, the role of granule size is very critical in the manufacturing process. Size affects mixing uniformity and content uniformity. Flowability of granules is also affected. Criticality was found at the 300-500 micron range of mean granule diameter, as well as with respect to tablet hardness and tensile strength. In the optimum 300-500 micron range, obtained at less than about 3% moisture content, apparently the granule size allows greater interparticle contact points per unit area, facilitating compression. A significantly greater mean granule diameter is obtained at 5% moisture.

6. The Hausner ratio measures the ability of the granule to flow during tabletting. Figure 3 shows that moisture content significantly affects the Hausner ratio, and thus the flowability of the granules. The sensitivity of this measurement is shown by the small scale of the Hausner ratio. Criticality was found at the less than 3% moisture levels, as optimal flow was observed at that level.

7. The compressibility index measures the ability of the granules to be compressed. There is a significant gradient between less than 3% and 5% as shown in Figure 4. Criticality was found at less than 3% moisture content. Optimum compressibility was observed at this level resulting in the minimum acceptable tablet hardness and tensile strength.

8. With respect to friability, there is a significant gradient between less than 3% and 5%, as shown in Figure 5. Criticality was found with regard to friability as less than 3% moisture gave less friable tablets that were easy to coat without abrasion or breaking during the coating process.

9. Moisture content significantly affected the hardness of a tablet as shown in Figure 6. There is an optimum level of hardness below which the performance of a tablet is compromised. This critical level was found to be reached at less than 3% moisture content. At 5% moisture content and greater, tablet hardness drops significantly to an unacceptable level.

10. Moisture content as shown in Figure 7 significantly affects the tap or packing density of a granule bed. The higher the moisture content, the lower the tap density. An optimum level of packing density was found, below which the physical performance of a granule is compromised. This critical level was found to be reached at less than 3% moisture content. At 5% moisture content and greater, the tap density drops significantly to an unacceptable level resulting in a bulky, more porous granule that needs more space during processing and filling operations.

11. Criticality was observed with regards to stability for certain moisture sensitive drug products. Moisture contents of less than 3% resulted in a more stable product than moisture contents of 5% and higher. The higher moisture content may lead to degradation during storage.

12. These results in moisture content effects, and the significant differences in properties obtained using less than 3% moisture content as compared with 5% moisture content, are unexpected in view of the three patent references cited above.

13. Isa Odidi and Amina Odidi further declare that all statements made herein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

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Isa Odidi

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Amina Odidi

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